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Influenza vaccine effectiveness: Maintained protection throughout the duration of influenza seasons 2010–2011 through 2013–2014

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ABSTRACT

Background: Factors, such as age, comorbidities, vaccine type, herd immunity, previous influenza exposure, and antigenic shift may impact the immune response to the influenza vaccine, protection against circulating strains, and antibody waning. Evaluating vaccine effectiveness (VE) is important for informing timing of vaccine administration and evaluating overall vaccine benefit.
Methods: VE was assessed using febrile respiratory illness surveillance among Department of Defense non-active duty beneficiaries from influenza seasons 2010–2011 through 2013–2014. Respiratory specimens were taken from participants meeting the case definition and tested by polymerase chain reaction for influenza. VE was calculated using logistic regression and by taking 1 minus the odds ratio of being vaccinated in the laboratory confirmed positive influenza cases versus laboratory confirmed negative controls.
Results: This study included 1486 participants. We found an overall adjusted VE that provided significant and fairly consistent protection ranging from 54% to 67% during 0–180 days postvaccination. This VE dropped to −11% (95% confidence interval: −102% to 39%) during 181–365 days.
Conclusions: Our study found moderate VE up to 6 months postvaccination. Since the influenza season starts at different times each year, optimal timing is difficult to predict. Consequently, early influenza vaccination may still offer the best overall protection.

1. Introduction

Each year roughly 5–20% of the US population is infected with influenza, resulting in an estimated 3000–49,000 deaths [1]. The best way to prevent influenza-associated disease burden is vaccination; therefore, as of 2010, influenza vaccination has been recommended for everyone in the United States, 6 months of age and older [2]. Yearly revaccination is necessary because circulating strains and/or vaccine composition change every influenza season. Additionally, previous studies have found that influenza vaccine effectiveness (VE) declines over time since vaccination in some populations does not provide significant protection in most cases after 90–120 days [3–7]. Many factors impact VE estimates and speed of decline – including age, comorbidities, herd immunity, use of adjuvants, type of vaccine administered (live attenuated or inactivated), prior natural influenza exposure, prior influenza vaccination, antigenic drift, and study design [6,8–13].

Previous studies have assessed influenza VE declines in relatively small sample sizes or from 1 influenza season [3–6,14]. Additionally, many of these studies have been conducted outside the United States, in regions that have different vaccine composition (adjuvant vs. non-adjuvanted) [6,15], and vaccine recommendations [2,16], and may also have differences in circulating strains and in the proportion of LAIV vs. IIV and quadrivalent versus trivalent vaccine which is administered. The goal of this study is to evaluate VE over time among US Department of Defense (DoD) beneficiaries during 4 influenza seasons. Gaining a better understanding of postvaccination immunity declines is important for evaluating the benefit of the vaccine and planning the timing of vaccine administration.

2. Methods

2.1. Study participants

Participants were selected from the Naval Health Research Center's (NHRC) febrile respiratory illness surveillance of DoD non-active duty beneficiaries. The surveillance sites included Naval

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Medical Center San Diego, California; Naval Branch Health Clinic Kearny Mesa, San Diego, California; Naval Hospital Camp Pendleton, Oceanside, California; and Captain James A. Lovell Federal Health Care Center, North Chicago, Illinois. The case definition for febrile respiratory illness is a person presenting at an outpatient health care facility with an oral temperature ⩾38.1 °C (100.5 °F) or subjective fever, and either cough or sore throat. A convenience sample of up to 20 cases per week per site were enrolled (with sampling dependent upon study staffing hours, resulting in a near random sample) with nasal, combination nasal/throat, or nasopharyngeal swabs during influenza seasons 2010–2011 through 2013–2014. Samples were frozen and sent to NHRC for testing every 1–2 weeks along with de-identified case data. Vaccine history, including vaccine type, and date of vaccination were collected from medical records and/or recall. Cases tested positive for influenza by real-time polymerase chain reaction (qPCR), and controls tested negative for influenza. Briefly, separate qPCR assays were performed for influenza A and B using standard extraction methods and with primers provided by the Centers for Disease Control. Influenza A positive samples were further tested by CDC primers to determine subtype [influenza A (H3N2) or A(pH1N1)]. Viral culture was performed on a subset of influenza-negative samples using a rhesus monkey kidney cell line to ensure that qPCR assays remained sensitive.

This study included participants enrolled during seasonal epidemic influenza periods, which were defined as times of consistent circulation and identification of influenza positive cases. Participants with unknown influenza vaccine status or known influenza vaccine status but unknown vaccine date were excluded, as were those vaccinated <15 days or >365 days before sampling.

This research was conducted in compliance with all applicable federal and international regulations governing the protection of human subjects in research (Protocol NHRC.2007.0024). Participants gave written informed consent or parental informed consent if underage. Since all specimens in this study were collected previously and were de-identified for the purposes of this study, the NHRC institutional review board committee classified this study as minimal risk, exempt from full committee review.

2.2. Statistical analysis

Chi-squared and analysis of variance tests were used to compare the characteristics of cases and controls (Table 1). VE was calculated using logistic regression and by taking 1 minus the odds ratio (OR) of being vaccinated multiplied by 100 in the cases versus controls. The following variables were assessed in the adjusted VE model: age group (0–4 years, 5–24 years, 25–49 years, 50–64 years, and ⩾65 years), gender, influenza season (2010–2011, 2011–2012, 2012–2013, 2013–2014), and calendar season (November–December, January–February, March–June). Confounders (>10% change in OR) or variables with $P < .05$ in the multivariate model were left in the final adjusted model. The final model adjusted for age group (0–4, 5–24, 25–49, 50–64, and >64 years), calendar season, and influenza season. Overall VE estimates were also stratified by participants who were 0–14, 15–30, 31–60, 61–90, 91–180, and 181–365 days postvaccination. Additionally, age group (0–4, 5–24, and ⩾25 years), type of vaccine (inactivated influenza vaccine [IIV] versus live-attenuated influenza vaccine [LAIV]), influenza subtype, influenza season, and month stratifications were run for 15–90, 91–180, and 180–365 days postvaccination (Supplementary Table 1 and Figs. 1–3). SAS version 9.3 was used for all statistical analyses (SAS Institute Inc., Cary, North Carolina).

3. Results

During the 4 influenza seasons examined for our study, 1720 participants meeting the febrile respiratory illness case definition were enrolled, with 198 were excluded due to incomplete vaccination history, 36 were excluded due to vaccination <15 days before diagnosis, 5 excluded due to vaccination >365 days after diagnosis. Among the remaining 1481 participants, 387 (26%) were cases (influenza qPCR positive), and 1094 (74%) were controls (influenza negative). Viral culture testing of a subset of qPCR-negative samples showed that qPCR sensitivity remained high (>99%) throughout the study. Twenty-four percent of the cases and 48% of the controls were vaccinated. Among those vaccinated, mean vaccination days were similar for cases (119 days) and controls (108 days) ($P = .063$). The percentage of participants receiving IIV vaccination was very similar in both groups, with 76% among cases and 79% among controls ($P = .471$). There were some differences in the proportion of cases versus controls across influenza seasons, likely suggesting differences in flu severity or vaccine match from season to season. The majority (53%) of the cases occurred in the 5–24 year age group. Both cases and controls had similar percentages of men and women ($P = .965$; Table 1).

Table 1
Descriptive characteristics among cases (influenza positive) and controls (influenza negative), excluding those <15 days or >365 days postvaccination, $n = 1481$.

Characteristic	Cases, $n = 387$ (%)	Controls, $n = 1094$ (%)	p value
Age group (years)			<0.001
0–4	72 (19)	400 (37)	
5–24	206 (53)	436 (40)	
25–49	67 (17)	161 (15)	
50–64	37 (10)	86 (8)	
>64	5 (1)	11 (1)	
Sex (% Men)	173 (45)	490 (45)	0.965
Influenza vaccine (% Yes)	91 (24)	521 (48)	<0.001
Mean ± SD vaccination days	119 ± 56	108 ± 52	0.063
Influenza vaccine type (% IIV)	69 (76)	407 (79)	0.471
Influenza season			<0.001
2010–2011	76 (20)	118 (11)	
2011–2012	94 (24)	211 (19)	
2012–2013	137 (35)	294 (27)	
2013–2014	80 (21)	471 (43)	
Calendar season			0.002
November–December	83 (21)	199 (18)	
January–February	199 (51)	487 (45)	
March–June	105 (27)	408 (37)	

Abbreviations: IIV, inactivated influenza vaccine; SD, standard deviation.

Age, influenza season, and calendar season were all statistically significant in the multivariate logistic regression model. Age group was the only variable that was also a confounder. During the 0–14, 15–30, 31–60, 61–90, and 91–180-day intervals, overall VE estimates were fairly constant, with VE estimates fluctuating from 53% to 67% and remaining significant. After 180 days, overall adjusted VE estimates dropped to −16% (95% confidence interval [CI]: −117% to 38%) (Supplementary Table 1 and Fig. 1).

Stratified analyses by vaccine type, age group, and influenza subtype revealed no significant differences between adjusted VE during the 15–90 and 91–180 days postvaccination time periods, with a marked decrease in VE after 180 days. Exceptions were seen in 2 subgroups (25 years of age and older; A/pH1N1 subtype) that did not show a marked decrease in VE point estimates after 180 days, although confidence intervals were wide for these intervals (Supplementary Table 1 and Fig. 1).

Our study found slightly lower adjusted VE point estimates later in the influenza season (March, April, May) compared with early in the influenza season (December, January, February), as the ratio for percent influenza positive between unvaccinated and vaccinated groups became incrementally smaller until being nearly identical in May (Fig. 2).

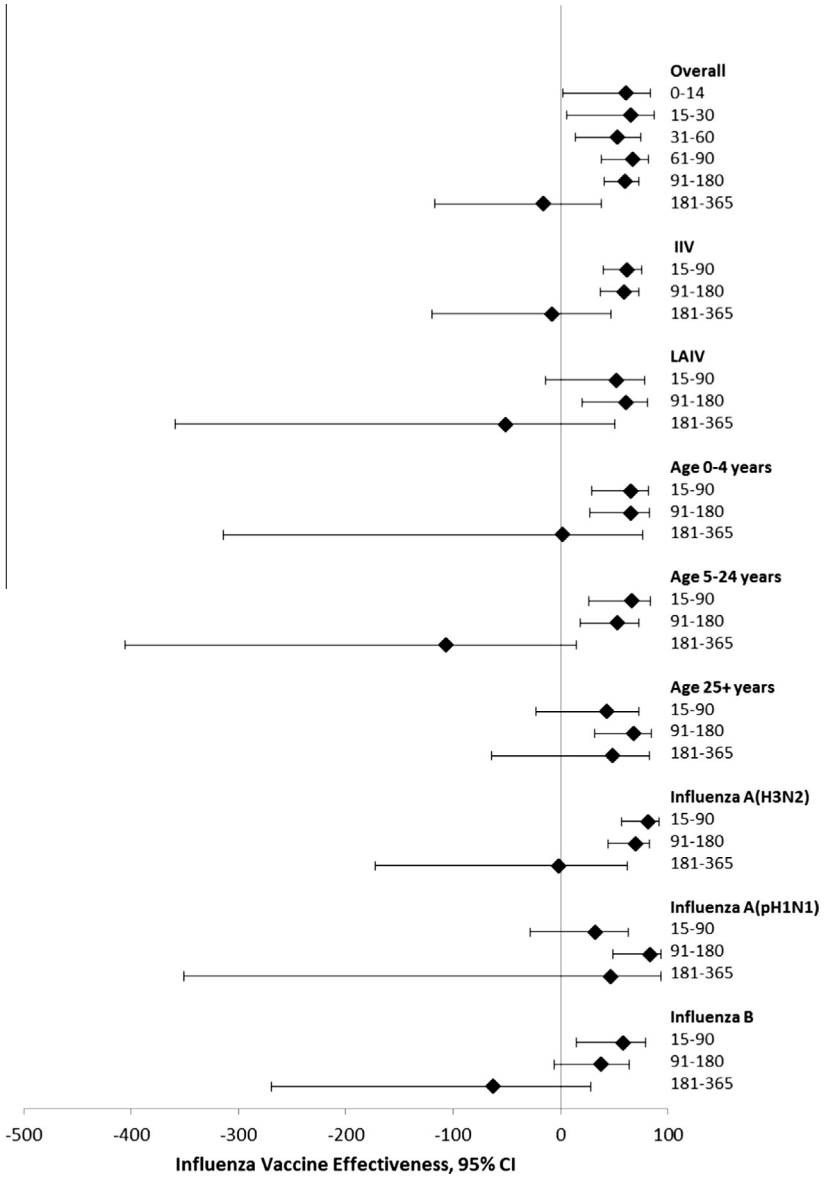

Fig. 1. Adjusted[a] influenza vaccine effectiveness[b] estimates (95% CI) by days postvaccination, overall and stratified by influenza vaccine type, age group, and influenza subtype. Data from 2010–2011 through 2013–2014. *Abbreviations:* CI, confidence interval; IIV, inactivated influenza vaccine; LAIV, live-attenuated influenza vaccine. [a]Logistic regression model adjusted for age group (0–4 years, 5–24 years, 25–49 years, 50–64 years, >64 years), calendar season (November–December, January–February, March–June), and influenza season (2010–2011, 2011–2012, 2012–2013, 2013–2014), unless already stratified by that variable. [b]Vaccine effectiveness = (1 − Odds Ratio) × 100.

When assessing VE estimates by influenza season, we found similar trends with higher protection during the 15–90 and 90–180-day periods compared with >180-day period. VE estimates during the 15–180-day period ranged from 54% to 70% and were statistically significant for all influenza seasons except 2010–2011 (Fig. 3).

4. Discussion

Comparing VE declines across studies can be difficult due to variations in vaccine group recommendations, type of vaccine used (adjuvanted versus unadjuvanted, IIV versus LAIV), herd immunity, prior vaccination, regional circulating strains, timing of the influenza season, vaccine match, and study design. Previous studies have found declines in VE for influenza A (H3N2) over time, with their VE estimates showing non-significant protection from the vaccine after several months [3–7] or evidence for increased infection with longer time since vaccination [14]. However, some of these studies had relatively small sample sizes and thus may have been underpowered to identify statistically significant VE even when it existed. This study is the first to assess waning influenza VE over time by examining 4 seasons of influenza data and looking at multiple subtypes in the United States.

Unlike prior VE studies, our study showed significant influenza vaccine protection up to 6 months postvaccination with only slight, but not significant, declines in some stratified VE estimates. The longer protection found in our study is supported by a similar study which found that influenza hemagglutinin (HA) and neuraminidase (NA) titers declined slowly over 18 months following influenza vaccination [17]. Surprisingly, our study even found moderate VE estimates during the first 2 weeks postvaccination, which is the period during which antibodies develop and HA and NA titers increase [1].

During 181–365 days postvaccination, our study showed significant declines in protection with overall adjusted VE equal to −16% (95% CI: −117% to 38%) (Table 1 and Fig. 1). Previous studies

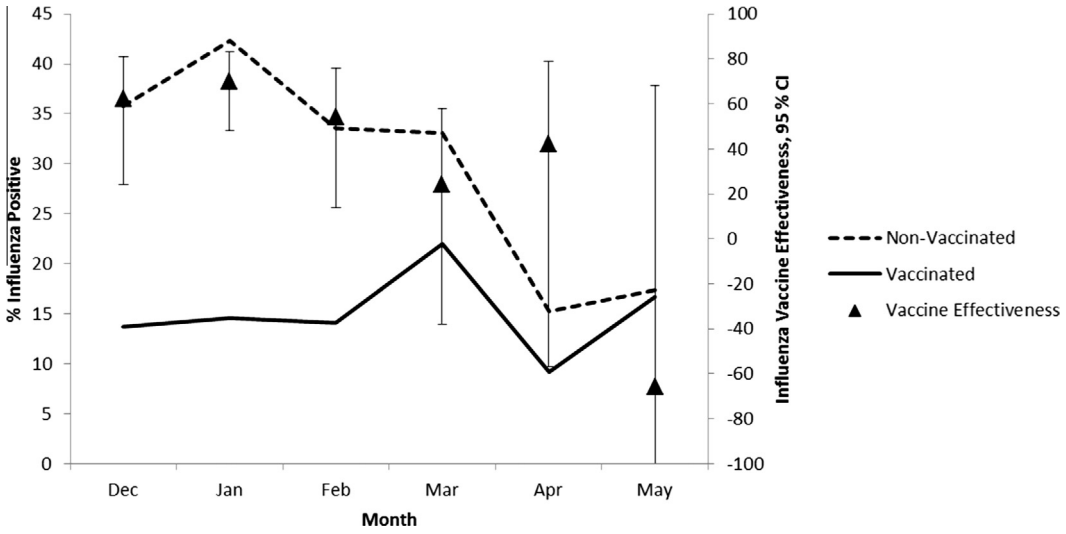

Fig. 2. Influenza percent positivity among vaccinated and non-vaccinated individuals and adjusted[a] influenza vaccine effectiveness with 95% CI, stratified by month of illness. *Abbreviation:* CI, confidence interval. [a]Logistic regression model adjusted for age group (0–4 years, 5–24 years, 25–49 years, 50–64 years, >64 years) and influenza season (2010–2011, 2011–2012, 2012–2013, 2013–2014). [b]Influenza vaccine effectiveness for May is equal to −66 (95% CI: −768 to 68). No vaccinated cases were identified in November or June.

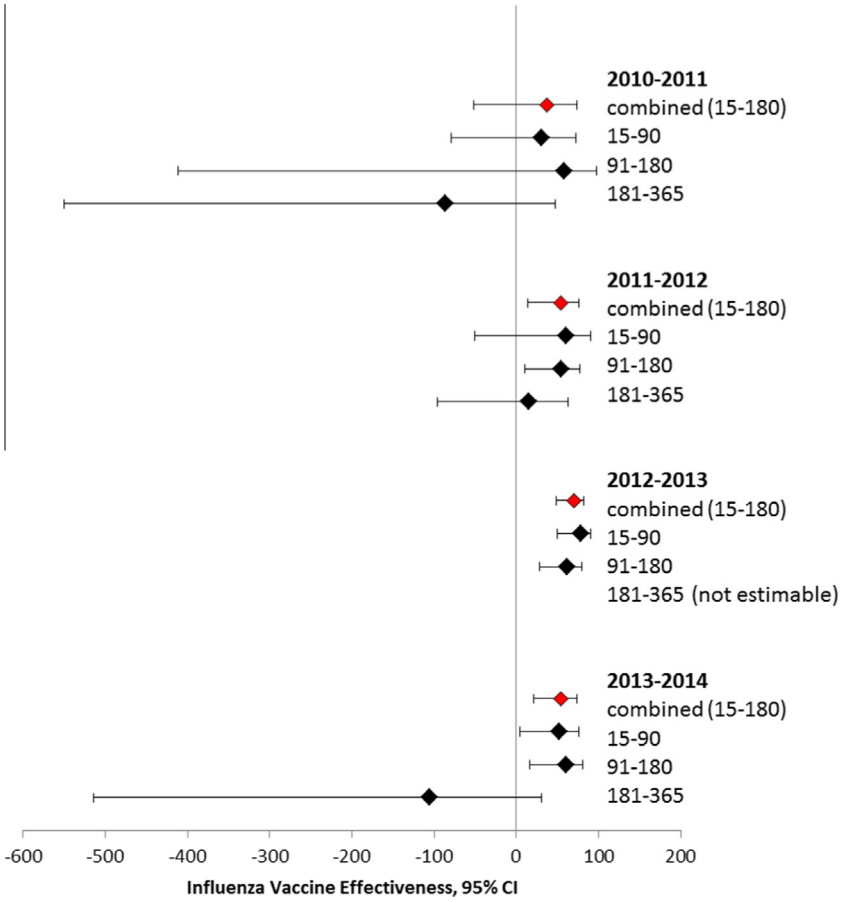

Fig. 3. Adjusted[a] influenza vaccine effectiveness[b] estimates (95% CI) by days postvaccination, stratified by influenza season. *Abbreviation:* CI, confidence interval. [a]Logistic regression model adjusted for age group (0–4 years, 5–24 years, 25–49 years, 50–64 years, >64 years) and calendar season (November–December, January–February, March–June). [b]Vaccine effectiveness = (1 − Odds Ratio) × 100. *Note:* Red dot indicates combined days post vaccination (15–180). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

assessing influenza protection beyond the season of vaccination have yielded mixed results. One study conducted in the United States found that the monovalent pH1N1 vaccine provided no protection from pH1N1 in the 2010–2011 influenza season [18]. However, another US study found similar VE estimates among those vaccinated in the previous season only compared with those vacci-

nated in the current season only [13]. Further studies may be necessary to evaluate protection ⩾6 months postvaccination.

Our results coincide with those of other studies, which have also found lower VE point estimates later in the influenza season. Previous studies have postulated that these declines are the result of antigenic drift or waning immunity [3–6]. Although percent positivity among vaccinated individuals remained relatively constant, the overall amount of circulating influenza was lower at the end of the season, reflecting the decline in VE estimates (Fig. 2).

Our study used a laboratory qPCR confirmed positive and negative control design of febrile respiratory cases presenting at outpatient clinics. This is a common method of collecting case and control data for VE studies, and is the method used by the CDC for their annual VE estimates [19]. Certain times of year may have less influenza and more other respiratory illness, therefore resulting in a greater number of controls and skewed VE estimates [20]. To deal with this, we restricted our analysis to periods of seasonal epidemic influenza periods.

There have also been mixed results for the effect of repeated vaccination on protection from influenza infection. One study found that participants, who were vaccinated in the current influenza season but infrequently vaccinated or not vaccinated in any of the previous 5 influenza seasons, had higher VE compared with those who were routinely vaccinated [13]. However, serological studies have not provided evidence for lower protection in those receiving routine annual influenza vaccinations [21]. Although we did not have data on prior vaccination history and were not able to control for it in our models, it is possible that this variable impacted our VE estimates.

Another potential reason for differences between our results and those of previous studies is variances in vaccine type and composition. Although our study showed similar VE estimates for IIV versus LAIV, previous studies have shown that LAIV produces significantly higher vaccine efficacy among children compared with IIV [9]. Additionally, the use of adjuvant in flu vaccines may play a role in VE estimates and comparability of our study with prior ones done in Europe: during the 2011–2012 influenza season, 2 adjuvanted vaccines were licensed for use in the European Union [15] and in the Kissling study, 4 of the 16 vaccines used contained adjuvant [6]. Previous studies have shown that adjuvanted vaccines result in significantly higher vaccine effectiveness than non-adjuvanted vaccines in the elderly [10,11]. Since adjuvanted vaccines are not licensed for use in the United States, we would have expected the other European studies to have slightly higher VE estimates over time than our study; however, this was not the case.

Differences in vaccination recommendations and coverage between the United States and other countries may also explain our study's higher VE estimates. The United States recommends universal influenza vaccination of all individuals older than 6 months of age [2]; whereas other countries, such as Spain, recommend the vaccine and offer it free of cost for people older than 60 years of age and those with risk factors [3,16]. Older populations are especially vulnerable to waning immunity after vaccination as a result of immunosenescence or deterioration of the immune system with age. If the elderly and people with comorbidities are more likely to get vaccinated than those without comorbidities, they may also be more likely to have impaired immune responses, thus biasing the VE estimates. Additionally, if less people overall are vaccinated, herd immunity will likely be lower in these populations, thereby also lowering VE estimates.

Variances in natural exposure to influenza and prior antibodies may influence immune response to the influenza vaccine and VE estimates, especially in the elderly. A study of elderly individuals who were seronegative before vaccination found that they did not accumulate enough antibodies from 1 vaccine influenza dose [12]. Another study found that low prevaccination antibody titers and greater age were associated with faster titer declines postvaccination [8]. Consequently, cohort effects might exist with certain age groups or with geographical populations having higher natural exposure or prior antibodies and therefore better protection against certain strains and improved response to the vaccine. We controlled for some of these factors by adjusting for age and influenza season in our model; however, we were not able to conduct elderly-stratified analyses due to the small sample size for this age group, as this study did not include any Veteran's Administration facilities that serve most of the retired military population.

The US Advisory Committee on Immunization Practices recommends that children who are aged 6 months through 8 years receive 2 doses of influenza vaccine [22]. However, in our study, only 27% of the children in this age range had received 2 doses of the influenza vaccine at the time of illness. Consequently, VE estimates for this age group are likely lower than if we had only included children who had completed the full vaccine course. Similarly, a high-dose influenza vaccine was recommended to individuals 65 years and older beginning in 2010–2011 and believed to improve protection in the elderly [23]. Unfortunately, we did not have data on the proportion who received the higher-dose vaccine.

Another limitation of our study is that we did not conduct a phylogenetic analysis of circulating strains to assess the degree of antigenic drift from year to year. This may be a factor which impacts declines in immunity over time. However, 1 study that performed a phylogenetic assessment of circulating strains did not find any antigenic drift at the end of the season, suggesting that the declines were a result of waning immunity [4]. Other studies have tried to assess the impact of antigenic drift by conducting a separate analysis for early and late season VE and have found lower VE in the late season, which may be reflective of antigenic drift [6]. We controlled for the potential impact of antigenic drift by adjusting for calendar season in our adjusted model.

This study gathered data from a well-established respiratory illness surveillance system. The consistency of this surveillance system allowed for robust comparisons across influenza seasons which have not been done before. When comparing influenza seasons, we found similar trends for each influenza season, with higher protection during 15–180 days postvaccination and declines after this period. We also observed lower VE estimates during the 2010–2011 season, which may correspond to antigenic drift of the pH1N1 strain during this influenza season [24] (Fig. 3).

Our results suggest that administering influenza vaccines closer to the start of the influenza season may increase VE slightly in some groups. However, we also found that the flu vaccine offered moderate and significant protection against influenza infection for the duration of the influenza season or up to 6 months postvaccination. Since the start of the flu season varies each year, it is somewhat difficult to predict the most opportune time to vaccinate each year. Consequently, early vaccine administration in the fall (before the start of the flu season) may still prevent the greatest number of influenza infections.

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This work was supported by the Armed Forces Health Surveillance Branch – Global Emerging Infections Surveillance and Response Section. The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the U.S. Government. Approved for public release; distribution is unlimited. U.S. Government Work (17 USC 105). Not copyrighted in the U.S. This research has been conducted in compliance with all applicable federal regulations governing the protection of human subjects in research (Protocol NHRC.2007.0024).

Conflicts of interest statement

None of the authors report any conflicts of interest.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2016.05.034.

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14. ABSTRACT

Background: Factors, such as age, comorbidities, vaccine type, herd immunity, previous influenza exposure, and antigenic shift may impact the immune response to the influenza vaccine, protection against circulating strains, and antibody waning. Evaluating vaccine effectiveness (VE) is important for informing timing of vaccine administration and evaluating overall vaccine benefit.

Methods: VE was assessed using febrile respiratory illness surveillance among Department of Defense non-active duty beneficiaries from influenza seasons 2010–2011 through 2013–2014. Respiratory specimens were taken from participants meeting the case definition and tested by polymerase chain reaction for influenza. VE was calculated using logistic regression and by taking 1 minus the odds ratio of being vaccinated in the laboratory confirmed positive influenza cases versus laboratory confirmed negative controls.

Results: This study included 1486 participants. We found an overall adjusted VE that provided significant and fairly consistent protection ranging from 54% to 67% during 0–180 days postvaccination. This VE dropped to −11% (95% confidence interval: −102% to 39%) during 181–365 days.

Conclusions: Our study found moderate VE up to 6 months postvaccination. Since the influenza season starts at different times each year, optimal timing is difficult to predict. Consequently, early influenza vaccination may still offer the best overall protection.

15. SUBJECT TERMS

vaccine effectiveness, influenza, postvaccination, age groups

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